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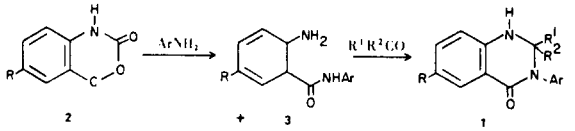
Received June 20, 1977

Details are given for the reaction of isatoic anhydrides with different primary aromatic amines to give several new *N*-aryl-*o*-aminobenzamides. The latter were annulated with a variety of dialkyl and alkyl aryl ketones to give 2,3-dihydro-4(1*H*)quinazolinones. Several novel and efficient procedures for effecting the cyclization are described.

J. Heterocyclic Chem., 14, 1357 (1977)

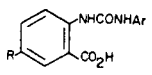
In an earlier paper (1), we reported the synthesis of a number of substituted 2,3-dihydro-4(1*H*)quinazolinones *via* the annulation of *N*-alkyl-, *N*-aryl-, and *N*-aralkyl-*o*-aminobenzamides with aromatic aldehydes. A number of those derivatives were found to be potent inhibitors of the multiplication of Earle's L cell line of mouse fibroblasts growing in suspension (2). In this paper, we are describing procedures for (i) preparing several other *N*-aryl-*o*-aminobenzamides and (ii) the cyclization of those intermediates with dialkyl and alkyl aryl ketones to give a variety of 2,2-disubstituted-2,3-dihydro-4(1*H*)quinazolinones, **1**.

A.though primary aliphatic amines react readily with isatoic anhydrides, **2**, to give high yields of *N*-alkyl-*o*-aminobenzamides, the more weakly basic aromatic primary amines react sluggishly with the same substrates and are reported to give complex mixtures of products (3). We are now describing procedures for this reaction that give **3**, along with by-product, **4**, in fair yields.



2 + **3** **1**

R = H, Cl
Ar = *o*-tolyl, *o*-chlorophenyl



4

11, R = H, Ar = *o*-tolyl, $R^1 = CH_3$, $R^2 = C_6H_5$
12, R = H, Ar = *o*-tolyl, $R^1 = CH_3$, $R^2 = n\text{-}C_5H_{11}$
13, R = Cl, Ar = *o*-tolyl, $R^1 = R^2 = CH_3$
14, R = H, Ar = *o*-tolyl, $R^1 = CH_3$, $R^2 = C_2H_5$
15, R = Cl, Ar = *o*-tolyl, $R^1 = CH_3$, $R^2 = C_2H_5$
16, R = H, Ar = *o*-tolyl, $R^1 = CH_3$, $R^2 = C_6H_5$
17, R = Cl, Ar = *o*-tolyl, $R^1 = CH_3$, $R^2 = C_6H_5$
18, R = H, Ar = *o*-tolyl, R^1 = Et, $R^2 = C_6H_5$
19, R = H, Ar = *p*-tolyl, $R^1 = CH_3$, $R^2 = C_6H_5$
20, R = Cl, Ar = *o*-tolyl, $R^1 + R^2 = (CH_2)_4$
21, R = H, Ar = *p*-tolyl, $R^1 + R^2 = (CH_2)_5$

In addition to the annulation procedures previously reported, we are now describing a novel and effecient cyclodehydration, namely that of employing *p*-toluenesulfonic acid as the catalyst in a 1:1 mixture of cyclohexane and alcohol as the reaction medium; the water formed in the reaction distilled as the ternary with that solvent mixture, with the water separating cleanly as the lower phase in the Dean-Stark still-head (4).

EXPERIMENTAL

The spectral and analytical data were obtained from the Analytical Department of This Institute as described in the earlier paper (1). The melting points were determined in capillary tubes in an electrically heated oil bath and are uncorrected.

N-(*o*-Chlorophenyl)-*o*-aminobenzamide (**5**) and 2-[[(*o*-Chlorophenyl)amino]carbomoyl]benzoic Acid (**6**).

A suspension of 69.0 g. (0.42 mole) of isatoic anhydride, 60.0 g. (0.47 mole) of *o*-chloroaniline, and 750 ml. of 95% ethanol was stirred and heated under reflux for 18 hours. The clear dark solution that had formed was concentrated to dryness *in vacuo*. The residual semisolid was filtered with suction through a coarse sintered glass funnel to remove 12.0 g. of unreacted isatoic anhydride. The liquid filtrate slowly crystallized, and that solid, 46.6 g., was distributed between 200 ml. of 5% aqueous potassium hydroxide and 250 ml. of methylene chloride by means of vigorous agitation. The two layers were separated, the lower aqueous phase was reextracted with 25 ml. of fresh methylene chloride, and the combined organic extracts were washed with water, dried, and concentrated to give 8.8 g. of crude **5**. The latter was heated briefly under reflux with 500 ml. of diisopropyl ether, the hot mixture was filtered, and the filtrate cooled to give 7.4 g. (8% yield) of **5**, m.p. 165-167°; ir (mull): ν 3400(m), 3250(m), 3200(m), 1670(s), 1625(m), 1580(s), 1525(s), 1475(s), 1460(s) cm^{-1}; pmr (deuteriochloroform): δ 6.50-7.85 (m, 7H, 7 Ar-*H*), 8.38-8.90 (m, 2H, NH_2), 11.60 (s, 1H, N*H*).

Anal. Calcd. for $C_{13}H_{11}ClN_2O$: C, 63.29; H, 4.49; N, 11.34. Found: C, 63.57; H, 4.22 N, 11.53.

The aqueous potassium hydroxide solution was neutralized with glacial acetic acid. The oil that separated slowly granulated; it was filtered and recrystallized from 400 ml. of acetonitrile to give 4.8 g. (4% yield) of **6**, m.p. 176-177° dec; ir (potassium bromide): ν 3400(s), 3280(s), 3100-2700(broad, m), 1690(s), 1665(s), 1605(s), 1595(m), 1580(s), 1540(s), 1480(s), 1440(s) cm^{-1}; pmr (DMSO-d_6): 5.93-7.35 (m, 8H, 8 Ar-*H*), 8.28 (s, 2H, 2N*H*), 9.28 (s, 1H, CO_2H) (both N*H* and CO_2H equilibrate with deuterium oxide).

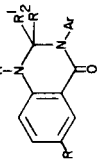
Anal. Calcd. for $C_{14}H_{11}ClN_2O_3$: C, 57.83; H, 3.82; N, 9.63. Found: C, 58.00; H, 3.83; N, 9.75.

N-(*o*-Tolyl)-*o*-aminobenzamide (**7**) and 2-[[(*o*-Tolyl)amino]carbamoyl]benzoic Acid (**8**).

A mixture of 41.0 g. (0.25 mole) of isatoic anhydride, 27.0 g. (0.25 mole) of *o*-toluidine, and 400 ml. of 95% ethanol were reacted as described for **5**. The clear solution was concentrated to dryness *in vacuo* and the residual semisolid was stirred vigorously with a solution of 110 ml. of concentrated hydrochloric acid (37%) in 1.5 l. of water. The suspended solid was filtered and air-dried to give 9.6 g. of solid (see below). To the filtrate was added, in portions, solid sodium carbonate to adjust the *p*H to 9. The precipitated solid was filtered, washed with water, and air-dried to give 44.0 g. of crude **7**, m.p. 99-100°. This was recrystallized from a mixture of 485 ml. of 2-propanol and 205 ml. of water to give 31.6 g. (56% yield) of **7**, m.p. unchanged at 99-100°; ir (potassium bromide): ν 3400(m), 3250(m), 3200(m), 1665(s), 1620(m), 1575(s), 1520(s), 1470(s), 1455(s) cm^{-1}; pmr (deuteriochloroform) δ 2.27 (s, 3H, CH_3), 5.25-5.80 (broad s, 2H, NH_2) (equilibrates with deuterium oxide), 6.50-8.00 (m, 9H, 8 Ar-*H* plus N*H*).

Table I

Substituted 2,3-Dihydro-4(1*H*)quinazolinones



Compound No.	Molecular Formula	Method	R	R^1	R^2	Ar	M.p. °C	Recrystallization Solvent	Yield, %	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
14	$C_{18}H_{20}N_2O$	C	H	CH_3	C_2H_5	*o*-tolyl	223-225	Ethyl acetate	55	77.11	7.19	9.99	77.02	7.24	9.96
15	$C_{18}H_{19}ClN_2O$	A	Cl	CH_3	C_2H_5	*o*-tolyl	212-215	Acetonitrile	50	68.69	6.08	8.89	68.81	5.82	9.13
17	$C_{22}H_{19}ClN_2O$	A	Cl	CH_3	C_6H_5	*o*-tolyl	189-191	2-Propanol	45	72.82	5.29	7.72	72.80	5.25	7.90
18	$C_{23}H_{22}N_2O$	A	H	C_2H_5	C_6H_5	*o*-tolyl	194-195	Cyclohexane	50	80.68	6.48	8.19	80.48	6.56	8.29
19	$C_{18}H_{20}N_2O$	A	H	CH_3	C_2H_5	*p*-tolyl	213-214	Acetonitrile	80	76.66	6.81	10.52	76.90	6.57	10.25
20	$C_{19}H_{19}ClN_2O$	A	Cl	$(CH_2)_4$		*o*-tolyl	228-230	Methylcyclohexane	75	69.81	5.86	8.57 (a)	70.09	5.59	8.63
21	$C_{20}H_{22}N_2O$	A	H	$(CH_2)_5$		*p*-tolyl	213-215	Methylcyclohexane	71	78.40	7.24	9.14	78.37	7.19	8.86

(a) Calcd: Cl, 10.84. Found: Cl, 11.11.

Anal. Calcd. for $C_{14}H_{14}N_2O$: C, 74.32; H, 6.24; N, 12.39. Found: C, 74.39; H, 6.26; N, 12.59.

The 9.6 g. of solid insoluble in aqueous hydrochloric acid (see above) was stirred with 100 ml. of 10% aqueous sodium hydroxide solution, filtered, and the filtrate neutralized with glacial acetic acid. The solid that separated was filtered and air-dried to give 5.0 g. of crude **8**, m.p. 171-172° dec. Recrystallization from 525 ml. of acetonitrile gave 3.5 g. (5% yield) of **8**, unchanged at 170-171° dec.; ir (potassium bromide): ν 3500-3375(broad, m), 3190(s), 3070(s), 2880(m), 1680(s), 1665(s), 1605(m), 1585(s), 1496(m), 1475(m), 1450(s), 1410(s) cm^{-1}; pmr (DMSO-d_6): δ 2.27 (s, 3H, C*H*$_3$), 6.90-8.47 (m, 8H, 8 Ar-*H*), 8.95 (s, 1H, N*H*), 10.28 (s, 1H, N*H*), 13.00-13.40 (broad s, 1H, CO_2H) (both NH and CO_2H signals aquilibrate with deuterium oxide).

Anal. Calcd. for $C_{15}H_{14}N_2O_3$: C, 66.65; H, 5.52; N, 10.37; N.E., 270. Found: C, 66.38; H, 5.31; N, 10.10; N.E. ($KOCH_3$), 268; N.W. (aq. NaOH), 274.

2-Amino-5-chloro-*N*-(*o*-tolyl)benzamide (**9**) and 5-Chloro-2-[[(*o*-tolyl)aminocarbomoyl]benzoic Acid (**10**).

A suspension of 99.0 g. (0.5 mole) of 6-chloroisatoic anhydride, 54.0 g. (0.5 mole) of *o*-toluidine, and 1 l. of 95% ethanol was stirred and heated under reflux as described for **5** and then concentrated to dryness *in vacuo*. The semisolid residue was stirred vigorously with a solution of 165 ml. of concentrated hydrochloric acid (37%) and 2.25 l. of water, the suspension that formed was filtered, the insoluble material was washed with 100 ml. of water, and air-dried (see below). The combined hydrochloric acid and water filtrates were cooled and neutralized with solid sodium carbonate. The solid that separated was filtered, dried, and recrystallized from acetonitrile (35 ml./g.) to give 46.8 g. (35% yield) of **9**, m.p. 173-174 dec.; ir (deuteriochloroform): ν 3490(w), 3430(w), 3360(w), 1610(m), 1575(s), 1550(m), 1510(s), 1485(s), 1445(s) cm^{-1}; pmr (deuteriochloroform): δ 2.30 (s, 3H, C*H*$_3$), 5.35-5.70 (broad s, 2H, N*H*$_2$), 6.60-7.90 (m, 8H, 7 Ar-*H* plus N*H*).

Anal. Calcd. for $C_{14}H_{13}ClN_2O$: C, 64.50; H, 5.02; N, 10.73. Found: C, 64.21; H, 4.82; N, 10.66.

The solid insoluble in hydrochloric acid was recrystallized from 2-propanol (70 ml./g.) to give 7.50 g. (5% yield) of **10**, m.p. 207-208° dec., ir (potassium bromide): 3700-3660 (broad, s), 1800 (broad, s), 1720(s), 1700(s), 1640(s), 1575(w), 1540(m), 1510(m), 1430(m), 1405(m) cm^{-1}; pmr (deuteriochloroform): δ 1.50 (s, 3H, C*H*$_3$), 6.10-7.55 (m, 7H, 7 Ar-*H*), 8.15(s, 2H, 2N*H*), 9.60 (s, 1H, CO_2H) (both N*H* and CO_2H equilibrate with deuterium oxide.

Anal. Calcd. for $C_{15}H_{13}ClN_2O_3$: C, 59.12; H, 4.30; N, 9.18; Cl, 11.62; N.E., 305. Found: C, 59.26; H, 4.25; N, 9.35; Cl, 11.44; N.E. ($KOCH_3$), 314.

2,3-Dihydro-2-ethyl-2-phenyl-3-(*o*-tolyl)-4(1*H*)quinazolinone (**11**) (Method A).

A solution of 2.26 g. (0.01 mole) of **7**, 4.0 ml. of propiophenone, 0.1 g. of *p*-toluenesulfonic acid (*p*-TSA), and 50 ml. each of cyclohexane and *t*-butyl alcohol was heated under a Dean-Stark trap for 4 hours, filtered, and the filtrate cooled to give 1.15 g. (35% yield) of **11**, m.p. 194-196°, that was analytically pure; ir (deuteriochloroform): ν 3405(w), 1650(s), 1620(s), 1590(m), 1520(m), 1490(s), 1450(s), 1420(m) cm^{-1}; pmr (deuteriochloroform): δ 0.77 [t(J = 7 Hz), 3H, C*H*$_3$CH$_2$], 2.10-2.30 (m, 5H, C*H*$_3$ plus CH$_3$C*H*$_2$), 4.70-5.20 (broad s, 1H, N*H*), 6.50-7.65 (m, 13H, 13 Ar-*H*).

Anal. Calcd. for $C_{23}H_{22}N_2O$: C, 80.68; H, 6.48; N, 8.19. Found: C, 80.48; H, 6.56; H, 8.29.

2,3-Dihydro-2-methyl-2-pentyl-3-(*o*-tolyl)-4(1*H*)quinazolinone (**12**) (Method B).

A solution of 2.26 g. (0.01 mole) of **7**, 5.0 ml. of 2-heptanone, 0.1 g. of *p*-TSA, and 50 ml. of anhydrous toluene was kept at ambient temperature for 8 days. During that time, there occurred the gradual development of a bright red color accompanied by the separation of a crystalline product. The solid was filtered and air-dried to give 1.70 g. of crude **12**, m.p. 145-147°. This was recrystallized from 21 ml. of acetonitrile to give 1.25 g. (39% yield) of 12, m.p. 151-153°; ir (potassium bromide): ν 3480(m), 3380(m), 3300(s), 1630(s), 1580(s), 1510(s), 1490(s), 1460(s) cm^{-1}; pmr (deuteriochloroform): δ 0.60-2.35 (m, 17H, 2(CH_3) plus C_5H_{11}), 4.65-5.15 (broad s, 1H, N*H*), 6.50-8.15 (m, 8H, 8 Ar-*H*).

Anal. Calcd. for $C_{21}H_{26}N_2O$: C, 78.23; H, 8.13; N, 8.68. Found: C, 77.96; H, 8.13; N, 8.54.

6-Chloro-2,3-dihydro-2,2-dimethyl-3-(*o*-tolyl)-4(1*H*)quinazolinone (**13**) (Method C).

To a solution of 3.0 g. (0.012 mole) of **9** in 100 ml. of acetone was added 0.1 g. of *p*-TSA. The product began to crystallize within 2 minutes. The mixture was kept for 4 days at ambient temperature and filtered to give 2.40 g. of air-dried solid; recrystallization from 135 ml. of acetonitrile gave 1.56 g. (52% yield) of **13**, m.p. 253-255°; ir (deuteriochloroform): ν 3500(w), 3405(m), 3300(m), 1715(m), 1650(s), 1615(s), 1585(m), 1490(s) cm^{-1}; pmr (deuteriochloroform): δ 1.22, 1.70, 2.17 [3 s, 9H, 3(CH_3)], 4.23-4.65 (broad s, 1H, N*H*), 6.50-7.90 (m, 7H, 7 Ar-*H*).

Anal. Calcd. for $C_{17}H_{17}ClN_2O$: C, 67.88; H, 5.70; N, 9.31. Found: C, 68.09; H, 5.65; N, 9.55.

2,3-Dihydro-2-methyl-2-phenyl-3-(*o*-tolyl)-4(1*H*)quinazolinone (**16**) (Method D).

A solution of 4.25 g. (0.02 mole) of **7**, 0.1 g. of *p*-TSA, 4.0 ml. of acetophenone, and 100 ml. of absolute ethanol was heated under reflux under anhydrous conditions for 28 hours, cooled, and the product that separated was filtered and air-dried to give 2.85 g. of crude **16**, m.p. 197-199°. Recrystallization from 120 ml. of 2-propanol gave 0.95 g. (11% yield) of **16**, m.p. 200-202°; ir (potassium bromide): ν 3300(s), 1630(s), 1580(m), 1510(s), 1495(s), 1460(m), 1445(m), cm^{-1}; pmr (deuteriochloroform): δ 1.60-1.95 (m, 3H, CH_3), 2.15-2.50 (m, 3H, CH_3), 5.25-5.50 (broad s, 1H, N*H*), 6.95-8.20 (m, 13H, 13 Ar-H).

Anal. Calcd. for $C_{22}H_{20}N_2O$: C, 80.46; H, 6.14; N, 8.52. Found: C, 80.33; H, 6.31; N, 8.53.

Data on the remaining compounds are summarized in Table I.

REFERENCES AND NOTES

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(3) R. P. Staiger and E. B. Miller, *J. Org. Chem.*, **24**, 1214 (1959); R. H. Clark and E. C. Wagner, *ibid.*, **9**, 55 (1953).

(4) "Azeotropic Data", Vol. 6 in "Advances in Chemistry Series," Industrial and Engineering Chemistry, Ed., American Chemical Society, Washington, D. C., 1952, p. 259. The composition of the ternary azeotrope is 8% water, 21% *t*-butyl alcohol and 71% cyclohexane; the supernatant in the Dean Stark trap contains $<1\%$ water.